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Article

Neuropsychological findings in adults with triple X syndrome

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Abstract: Background: Triple X syndrome (TXS, also known as trisomy X or 47,XXX) has been associated with impaired overall neurocognitive functioning in children and relatively young adults. However, neurocognitive functioning in adults with TXS is poorly understood. The aim of this study was, therefore, to examine cognitive functioning in adults with TXS. Methods: In this cross-sectional study, data were collected from 34 adult women with TXS (mean age = 32.9; SD = 13.1) and 31 controls (mean age = 34.9; SD = 13.7). General intellectual functioning, semantic/verbal memory, visual/episodic memory, psychomotor speed, and attention and executive functioning were then compared between these two groups. Results: We found that general intellectual functioning was significantly lower in the TXS group compared to the control group. In addition, women with TXS had more attention problems and lower psychomotor speed, particularly motor processing speed. When the analyses were adjusted for IQ, the strength of these associations decreased. The women in the TXS group also scored significantly lower at free recall in the verbal memory test, but not in immediate or delayed recognition. Finally, visual/episodic memory and executive functioning did not differ significantly between groups. Conclusions: Our analysis revealed that women with TXS score lower in general intellectual functioning and have impairments in motor processing speed and attention compared to controls, but do not differ with respect to executive functioning. These results offer new insights for improving the support of adults with TXS both at school and in the workplace.

Keywords: Triple X syndrome; Adults; Neurocognitive functioning; Sex Chromosomal Disorders; Attention; Psychomotor speed; Executive functioning

1. Introduction

Triple X Syndrome

Females with triple X syndrome (TXS, also known as trisomy X) have a 47,XXX chromosome count rather than the standard 46,XX chromosome count. An estimated 1:1000 girls are born with TXS. Girls and young adults with TXS are relatively tall, have delayed motor milestones, poor coordination, and delayed language development [1]. Subfertility is also relatively common among women with TXS [2]. Other characteristics include a slightly increased prevalence of seizures and urogenital abnormalities [3]. In addition, girls and women with TXS have an increased prevalence of psychiatric disorders such as

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anxiety, depression, and psychotic disorders [4]. Finally, social impairments have been described in both children and adults with TXS [5].

General intellectual functioning

Previous studies in children [6,7] showed that compared to controls, girls with TXS have significantly lower Full-Scale IQ (FSIQ), VIQ (verbal IQ), and PIQ (performance IQ) scores, measured using the Wechsler Intelligence Scale for Children – Revised (WISC-R) [8]. Among a group of adolescents and young adults with TXS (aged 11-24), FSIQ ranged from 53-112 and IQ scores were clustered in the 85-90 range, significantly lower than in siblings [9]. The range is similar to the range in the general population, but the TXS group is skewed to the left in comparison with the control group [1,9].

In adolescents and adults, only one very small study was performed [10,11]. In this study, selection bias was a consequence of an unknown number of the girls that died during childhood. Another unknown number of girls were lost to follow-up [10]. Adolescents with TXS (n = 11) aged between 16 and 19 years who were assessed using the Wechsler Adult Intelligence Scale – Revised (WAIS-R) [12] had lower FSIQ scores than controls (n = 13) (TXS mean = 81.8; SD = 15.6; controls mean = 108.2; SD = 15.8) [11]. At follow-up, these participants were adults aged between 26-36 years, hereafter referred to as relatively young adults (mean = 31.1, SD= 2.55) [10]. The differences between the TXS (n = 11) and the control group (n = 16) were again statistically significant (FSIQ: TXS mean = 81.8; SD= 4.69; range = 62 – 121, vs. controls mean = 108.27; SD = 3.81, $p < .05$) [13]; VIQ: TXS mean = 78.7; SD = 5.34, vs. controls mean = 105.7; SD = 4.36, $p < .05$ and PIQ: TXS mean = 85.5; SD = 4.05 vs. controls mean = 109.9; SD = 3.31; $p < .05$) [10]. So, these differences in FSIQ, VIQ and PIQ between the TXS and control groups can persist into adulthood [10], but confirmation of this conclusion requires research in a larger unbiased group of participants.

Other neuropsychological domains

More recently, a broader computerised assessment using the Amsterdam Neuropsychological Tasks (ANT) [14] in a relatively small sample of children with an extra X chromosome (girls with TXS (n = 17; age = 12.20; SD = 2.56) and boys with 47,XXY, also known as Klinefelter syndrome (n = 23; age = 13.52; SD = 3.12) revealed no significant differences between these two groups of children and two groups of control children with respect to information processing speed, focused attention, or verbal working memory [15]. There were significant differences in FSIQ results between the extra X group and the control group. Interestingly, however, the authors found significant differences between the children with an extra X chromosome and controls with respect to sustained attentional control, inhibition, mental flexibility, and visual working memory. Importantly, they found that psychomotor speed was significantly lower in girls with TXS compared to boys with Klinefelter syndrome [15].

In contrast, studies involving adults with TXS are far scarcer than studies involving children and/or adolescents with TXS. We previously mentioned that in adolescents and adults, only one longitudinal small and biased study [10] was performed. In 1993, Bender et al. examined this cohort of adolescents with TXS [16] and found deficits in attention, concept formation, mental flexibility, spatial thinking, verbal fluency, and basic academic skills, as well as relatively strong verbal learning skills [16]. In 2001, this group subsequently reported that women aged 26-36 years scored significantly lower than controls on Information, Vocabulary, and Object Assembly measured using the WAIS-R [13]. However, they found no difference between adults with TXS and controls with respect to the Picture Completion subtest, which measures visual memory, recognition, and organisation [13]. Using the Wisconsin Card Sorting Test (WCST, which measures conceptual problem-solving abilities), and tests designed to assess reading and comprehension skills, the authors found that women with TXS performed significantly worse than controls after adjusting for FSIQ as a confounding factor [13]. This strategy was used to assess whether differences in individual measures were based on specific impairments, independent of overall intellectual ability [13]. Taken together, these early results suggest that

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neurocognitive functioning, with the exception of visual memory, recognition, and organisation are reduced in relatively young adults with TXS.

Neurocognitive functioning in adults with a neurodevelopmental disorder may reveal differences compared to neurocognitive functioning in childhood and adolescence, so separate studies in adults are warranted. To explain this possibility, it is important to acknowledge that cognitive impairments experienced during childhood may affect the development of other functions (e.g. an impairment in sustained attention may affect the ability to learn to read) [17]. For example, reduced reading skills may have consequences for general cognitive development. Another explanation may be related to the maturation and ageing of the brain. For example, maturation of the brain and brain plasticity may underlie the development of cognitive functioning during adulthood [18], and this development may be sex-specific [19]. In addition, maturation of the brain – and subsequent cognitive development – may also depend on extrinsic factors such as early intervention involving training of social functioning and/or additional support provided at school [20]. In TXS, cognitive functioning may be affected throughout the individual's lifespan, similar to findings in individuals with trisomy 21 [21]. In addition, psychotic disorders have been reported in individuals with TXS [1,4] and may also reduce cognitive functioning throughout life, similar to reports of subjects with 22q11 deletion syndrome [22]. To date, however, the effects of maturation and ageing on cognitive functioning in TXS have not been investigated, yet this information is urgently needed in order to support adults with TXS and answer parents' questions after they receive a prenatal or postnatal diagnosis of TXS for their child. Moreover, girls with TXS may wish to better understand whether their impairments will persist into adulthood.

The aim of this study was to examine differences in cognitive functioning between adult women with TXS and controls. Specifically, we tested the hypothesis that general intellectual function is lower in women with TXS compared to controls. In addition, we tested the hypothesis that women with TXS have reduced visual/episodic memory, semantic/verbal memory, attention, psychomotor speed, and executive functioning compared to controls.

2. Materials and Methods

2.1. Study design and setting

This was a cross-sectional study including both women with TXS and controls from the Flemish region of Belgium (Flanders) and the Netherlands.

2.2. Ethics

This study was performed in accordance with the ethical standards of the relevant national and institutional committees regarding human experimentation, and with the Declaration of Helsinki. All procedures involving human subjects were approved by the medical ethics committee at Maastricht University Medical Centre (MUMC+) and Maastricht University (approval number: NL46871.068.14/METC143051), and all participants provided written informed consent.

2.3. Participants

A total of 65 adult women (18-63 years of age) participated in the study, including 34 women with TXS (defined as having a 47,XXX chromosomal composition determined using conventional karyotyping) and 31 controls. Women with a mosaic chromosome count were excluded from the study [23]. In order to be eligible to participate in this study, subjects had to be both capable and competent to provide informed consent and had to be sufficiently proficient in the Dutch language. Women who were under legal guardianship at the time of the study were excluded for they were unable to provide independent consent. Two women were excluded for this reason. All 65 participants had a Caucasian background. To assess whether the postnatally diagnosed subgroup functioned at a lower level than the prenatally diagnosed subgroup due to ascertainment bias, we analysed the FSIQ results separately for these two groups.

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2.4. Procedure

Participants with TXS were recruited via flyers, digital newsletters, social media, the Dutch TXS support group (Contactgroep Triple-X Syndroom) and advertising. In addition, the Department of Clinical Genetics at MUMC+ maintains a list of women with TXS who have indicated they are willing to be approached for participating in scientific research; these women received a letter with an informational flyer and an invitation to participate in this study. Controls were recruited by asking families and friends of women with TXS and by advertising. Whenever possible, all assessments in one participant were performed on the same day.

2.5. Instruments

Two instruments were used to assess cognition, the Cambridge Neuropsychological Automated Test Battery (CANTAB) [24] and a brief version of the Wechsler Adult Intelligence Scale-III (WAIS-III) [25]. These instruments were used to assess various neuropsychological domains as described below. The Adult Behaviour Checklist (ABCL) [26] was used to assess behavioural problems that might be associated with attention problems.

2.5.1. General intellectual functioning

First, the highest levels of education achieved by the participants were enquired. Second, the brief version of the WAIS-III [25] was used to measure differences in general intellectual function. This version was used to prevent participants from leaving the study prematurely, as it is our clinical experience that women with TXS have reduced mental stamina. This brief version of the WAIS-III consists of four subtests, three of which are abbreviated versions of the original WAIS-III subtests, one is unabbreviated, namely the Digit Symbol Coding subtest, which was used to asses psychomotor speed. The Block Design subtest was used to assess spatial visualisation ability and motor skill. The Information subtest was used to assess general knowledge. Finally, the Arithmetic subtest was used to assess quantitative reasoning and working memory.

2.5.2. Other neuropsychological domains

The CANTAB was used to measure cognition. This test battery covered the following cognitive domains: attention and psychomotor speed, semantic/verbal memory, visual/episodic memory, and executive functioning. Details regarding the tests and subdomains are provided in the online supplemental materials and are available online [24].

2.5.2.1. Psychomotor speed

First, the Digit Symbol Coding subtest of the WAIS-III was used to assess psychomotor speed. Second, two CANTAB subtests were used to assess psychomotor speed, namely the Motor screening test (MOT) [27] and Reaction Time (RTI) [28]. The MOT subtest was used to assess sensorimotor skills and comprehension. This was the first test of the battery and was used to assess the capability to participate in a computer-based assessment. The RTI subtest was used to assess reaction time and movement time. Reaction time refers to the speed with which the subject releases a button at the bottom of the screen following the onset of a stimulus. In contrast, movement time refers to the time taken to touch the stimulus after the button has been released.

2.5.2.2. Verbal memory

Two CANTAB subtests were used to assess verbal memory, namely the Dutch versions of the Verbal Recognition Memory – Immediate recall and recognition test (VRM-I) [29] and the Verbal Recognition Memory – Delayed recall and recognition test (VRM-D) [29]. These subtests are part of the CANTAB memory domain.

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2.5.2.3. Visual information processing

The Block Design subtest of WAIS-III was used to assess visual information processing. A subtest of the CANTAB, namely the Paired Associates Learning (PAL), was also used to assess visual information processing [30].

2.5.2.4. Attention

Another CANTAB subtest was used to assess sustained attention, namely the Rapid Visual Information Processing (RVP) subtest [31]. The ABCL [26] was used to assess behavioural problems that might be associated with attention problems. The ABCL consists of 134 items based on behavioural problems during the past six months. The ABCL was scored by an individual who knew the participant well using a three-level rating scale ('absolutely not true', 'somewhat or sometimes true', and 'very true or often true') [26] with a higher score representing an increased level of problem behaviours. The Attention syndrome scale included 17 items such as 'Can't concentrate, can't pay attention for long' and 'Daydreams or gets lost in her thoughts'. The syndrome scales of the ABC discriminate between participants who have or have not any attentional problems [32]. Items on the Inattention scale (e.g. 'Fails to finish things she should do' and 'Poor work performance') and Hyperactivity-Impulsivity scale (e.g. 'Can't sit still, restless, or hyperactive' and 'Impulsive or acts without thinking') were combined in a sum score: the Attention Deficit Hyperactivity Disorder (ADHD) scale. The ADHD syndrome scale was used to assess whether criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) were met [33]. The DSM-oriented scales are based on experienced mental health professionals' ratings of the consistency of the problem items and the DSM-IV [32]. Norms differ based on age, with different norms for participants aged between 18 and 35 years and participants aged between 35 and 59 years [26]. Therefore, raw scores were converted to age-independent T-scores. T-scores were converted into three behavioural categories (normal, borderline, and clinical range). We present T scores and three behavioural categories.

2.5.2.5. Executive functioning

Executive functioning can be divided into the following subdomains: mental flexibility, planning, strategy, and response inhibition. The CANTAB subtests that were used to assess executive functioning were the Spatial Working Memory (SWM) subtest [34], the One Touch Stockings of Cambridge (OTS) subtest [35] and the Intra-Extra Dimensional Set Shift (IED) subtest [36]. The SWM subtest was used to assess strategy and working memory, the OTS subtest was used to assess spatial planning and working memory, and IED subtest was used to assess mental flexibility.

2.5.3. Statistical analyses

Continuous, normally distributed data were compared between groups using a two-tailed Student's *t*-test. Categorical data (i.e. education and clinical, borderline and normal ranges in the ABCL data) were analysed using the Fisher's exact test. T-scores for the ABCL Attention syndrome scale and the DSM-oriented ADHD scale were analysed using a two-tailed Student's *t*-test. The association between TXS and the ABCL T-scores were analysed using linear regression analysis adjusting for IQ. Spearman's rank correlation coefficients (r_s) were calculated between FSIQ and level of education.

Z-scores of the residuals of every CANTAB subtest score were calculated to identify potential outliers, which were then excluded from our analysis; Z-scores lower than -2.58 or higher than 2.58 were considered outliers [37]. Finally, linear regression analysis was performed to analyse the putative association between TXS and CANTAB; IQ was included in the analysis as a confounder. All statistical analyses were performed using STATA/MP for Mac, version 13.1 (StataCorp, College Station, TX). All analyses were two-tailed, and alpha was set at .05.

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3. Results

3.1. Population

The age of the participants (18-63 years of age) was not significantly different between the TXS and control groups, with mean age of 32.9 and 34.9 years (SD=13.1 and 13.7), respectively ($t(63) = -.59$, $p = .56$). Among the 34 women with TXS, 10 were diagnosed prenatally (mean age = 26.1 years, SD= 9.1), while the remaining 24 were diagnosed postnatally. The indications for postnatal testing included infertility/recurrent abortions (n=9; mean age = 44.3 SD= 9.4); atypical development (n=6; mean age = 28.5 SD= 11.5); history of a family member with a genetic condition (n=4; mean age = 45.8, SD= 11.7); small head (n=2); intestinal malformation (n=1); nuchal oedema (n=1); and epicanthal folds (n=1). Moreover, 73.5% and 80% of the participants in the TXS and control groups, respectively, were premenopausal at the time of the data collection. The number of the participants that used psychotropic medication was three in the TXS and three in the control group.

3.2. General intellectual functioning

The highest levels of education achieved by the women in the TXS and control groups are summarised in Table 1, showing that the women with TXS achieved a significantly lower level of education compared to controls.

Two of the participants in the TXS group declined to complete the WAIS-III due to unpleasant experiences during previous assessments of FSIQ. The results of the WAIS-III short version are summarised in Table 2, showing that FSIQ differed significantly between the TXS and control groups. Specifically, three of the four subtests differed significantly between groups, but the Arithmetic subtest did not. In addition, in the TXS group FSIQ was similar between the women who were diagnosed prenatally (86.7 SD= 7.6) and the women who were diagnosed postnatally (85.9, SD= 11.5; $t(30) = .19$, $p = .85$, data not shown). Lastly, we found a significant correlation between the FSIQ and the level of education in the TXS group ($rs = .47$, $p = .007$), and in the control group ($rs = .40$, $p = .027$).

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Table 1. Level of education in the women in the triple X syndrome (TXS) and control groups.

	TXS group (n = 34)	**Control group (n = 31)**
Lower than secondary vocational education	9 (26.47%)	1 (3.23%)
Secondary vocational education	20 (58.82%)	21 (67.74%)
Higher than secondary vocational education	5 (14.71%)	9 (29.03%)

Table 2. Summary of the results of the abbreviated WAIS-III in the triple X syndrome (TXS) and control groups.

	TXS group (n = 32)			**Control group (n = 31)**					
	Mean	**SD**	**95% CI**	**Mean**	**SD**	95% CI	*p*-value†	Effect size‡	95% CI
Full-scale IQ§	86.09	10.46	82.32, 89.87	96.77	12.69	92.12, 101.43	**.0005**	-0.92	-1.44, -0.40
Block Design¶	8.5	2.74	7.51, 9.49	10.13	3.22	8.95, 11.31	**.03**	-0.55	-1.05, 0.04
Digit Symbol Coding¶	8.47	2.54	7.55, 9.38	10.48	2.71	9.49, 11.48	**.003**	-0.77	-1.28, -0.25
Arithmetic¶	6.75	2.82	5.73, 7.77	8.06	2.48	7.16, 8.97	.05	-0.50	-0.99, -0.01
Information¶	8.16	2.41	7.29, 9.03	9.90	2.96	8.82, 10.99	**.01**	-0.65	-1.15, -0.14

† Students *t*-test
‡ Cohen's d
§ IQ estimate after transformation of WAIS estimation total score
¶ Scaled scores considering age
Abbreviations: WAIS-III - Wechsler Adult Intelligence Scale-III; 95% CI - 95% Confidence Interval; SD - Standard Deviation; IQ - Intelligence Quotient.

3.2. CANTAB

Every participant demonstrated enough competencies to use a computer-based assessment tool. One participant in the TXS group left the study before completing the CANTAB. Table 3 summarises the results on the CANTAB subtests in the TXS and control groups, and Table 4 summarises the results after adjusting for FSIQ as a potential confounder. Table 3 provides the actual numbers of participants for every CANTAB subtest in the TXS and control groups which makes clear that there were up to three outliers in the TXS group and up to two outliers in the control group. Results of the CANTAB subscales are described below.

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Table 3. Summary of the CANTAB test results in the triple X syndrome (TXS) and control groups.

	TXS				Controls					
Description	**N**	**Mean**	**SD**	**95% CI**	**N**	**Mean**	**SD**	**95% CI**	**t-value**	**p-value†**
Screening/familiarisation test: Motor screening (MOT).										
MOT Mean latency (ms): reaction time plus movement time; lower is better	34	709.38	133.88	661.91, 756.86	31	599.99	132.47	551.40, 648.58	3.28	**.0017**
MOT Mean error: lower is better	31	9.94	3.05	8.88, 11.01	31	9.80	1.95	9.08, 10.51	0.23	.82
Attention and psychomotor speed: Reaction Time (RTI).										
RTI Mean simple reaction time: Lower is better	32	291.92	30.71	280.85, 302.99	30	272.61	32.41	260.51, 284.72	2.41	**.019**
RTI Mean five-choice reaction time (ms): Lower is better	32	305.43	32.59	293.68, 317.18	30	295.67	26.40	285.81, 305.53	1.29	.20
RTI Mean simple movement time (ms): Lower is better	33	274.09	50.74	256.10, 292.08	31	223.62	44.50	207.30, 239.94	4.22	**.0001**
RTI Mean five-choice movement time (ms): Lower is better	32	286.35	52.83	267.30, 305.39	31	243.07	46.54	225.99, 260.14	3.45	**.001**
Attention and psychomotor speed: Rapid Visual Information Processing (RVP).										
RVP A′ prime: Range 0.0 to 1.0; bad to good	33	0.86	0.04	0.85, 0.87	31	0.89	0.04	0.88, 0.91	-3.32	**.0015**
RVP Mean Latency (ms): Lower is better	32	511.93	87.71	480.30, 543.55	30	445.72	61.23	422.86, 468.59	3.42	**.0011**
Visual memory test: Paired Associates Learning (PAL).										
PAL Total errors (adjusted): Lower is better	32	16.41	10.03	12.79, 20.02	30	15.07	12.13	10.54, 19.60	0.48	.63
Semantic/verbal memory test: Verbal Recognition Memory – Immediate (Dutch version) (VRM-I).										
VRM Free recall total correct: Higher is better	33	6.76	2.00	6.05, 7.47	30	7.9	7.9	7.28, 8.52	-2.46	**.017**
VRM Recognition total correct: Higher is better	33	22.76	1.39	22.26 - 23.25	30	22.93	1.08	22.53 - 23.34	-0.56	.58
Semantic/verbal memory tests: Verbal Recognition Memory (VRM) – delayed test (Dutch version) (VRM-D).										
VRM-2 recognition total correct: Higher is better	33	22.61	1.37	22.12 - 23.09	30	23	0.91	22.33 - 23.340	-1.33	.19
Executive function: Spatial Working Memory (SWM).										
SWM Total errors: Lower is better	34	11.74	11.93	7.57 - 15.90	31	9.39	7.15	6.76 - 12.01	0.95	.35
SWM Strategy: Lower is better	33	15.73	3.79	14.38 - 17.07	31	14.23	2.96	13.14 - 15.31	01.76	.08
Executive function: One Touch Stockings of Cambridge (OTS).										
OTS Problems solved on first choice: Higher is better	34	10.29	2.86	9.30 - 11.29	30	10.7	2.11	9.91 - 11.49	-0.64	.53
Executive function: Intra/ Extradimensional Set Shift (IED).										
IED errors Lower is better	33	7.85	7.81	5.08 - 10.62	29	7.17	7.93	4.15 - 10.19	0.34	.74
IED Total errors adjusted Lower is better	32	20.47	15.35	14.93 - 26.00	30	25.2	21.79	17.06 - 33.34	-0.99	.32

†. Students *t*-test.

Abbreviations: 95% CI - 95% Confidence Interval; SD - Standard Deviation; ms – milliseconds.

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Table 4. Summary of groups differences on cognitive functioning considering FSIQ as a potential confounder.

	B-value	t-value	*p*-value	95% CI	partial eta-squared (η_p^2)
Screening/familiarisation test: Motor screening (MOT).					
MOT Mean latency (ms)	-134.98	-3.58	**.001**	-210.32, -59.64	.18
MOT Mean error	0.32	0.46	.65	-1.07, 1.71	.04
Attention and psychomotor speed: Reaction Time (RTI).					
RTI Mean Simple reaction time (ms)	-13.08	-1.49	.14	-30.70, 4.55	.04
RTI Mean 5-choice reaction time (ms)	-6.67	-0.80	.43	-23.47, 10.12	.01
RTI Mean simple movement time (ms)	-42.25	-3.23	**.002**	-68.39, -16.11	.15
RTI Mean 5-choice movement time (ms)	-38.91	-2.81	**.007**	-66.64, -11.18	.12
Attention and psychomotor speed: Rapid Visual Information Processing (RVP).					
RVP A'Prime	0.02	2.11	**.04**	0.001, 0.044	.07
RVP Mean Latency (ms)	-64.99	-3.04	**.004**	-107.72, -22.26	.14
Visual memory test: Paired Associates Learning (PAL)					
PAL Total errors (adjusted)	-1.70	-0.53	.60	-8.10, 4.71	.05
Semantic/verbal memory test: Verbal Recognition Memory – Immediate (Dutch version) (VRM-I).					
VRM Free recall total correct	0.85	1.77	.08	-0.11, 1.81	.05
VRM Recognition total correct	-0.71	-0.21	.84	-0.76, 0.62	.00
Semantic/verbal memory tests: Verbal Recognition Memory – delayed test (Dutch version) (VRM-D).					
VRM-2 recognition total correct:	0.32	0.96	.34	-0.34, 0.98	.16
Executive function: Spatial Working Memory (SWM)					
SWM Total errors	0.28	0.10	.92	-5.13, 5.69	.00
SWM Strategy	-1.34	-1.47	.15	-3.17, 0.48	.04
Executive function: One Touch Stockings of Cambridge (OTS)					
OTS Problems solved on first choice	-0.34	-0.51	.61	-1.67, 0.99	.04
Executive function: Intra/ Extradimensional Set Shift (IED)					
IED EDS errors	0.62	0.28	.78	-3.76, 4.99	.01
IED Total errors adjusted	6.53	1.23	.22	-4.08, 17.15	.03

Abbreviations: FSIQ - Full-Scale Intelligence Quotient;.

3.2.1. Psychomotor speed

The Digit Symbol Coding subtest (for results see Table 2) had the largest effect size among the four subtests of the WAIS-III (Cohen's d = -.77). Our analysis revealed that the results of the MOT mean latency and the results of the RTI movement time differed significantly between the TXS and control groups, even after adjusting for FSIQ (Table 3 and Table 4). In contrast, the results of the MOT mean error did not differ significantly between the TXS and control groups. When FSIQ was added to the regression model as a potential confounder, the results of the RTI reaction time did not remain significantly different between the two groups.

3.2.2. Verbal memory

Our analysis revealed that the results of the VRM-I recall subtest differed significantly between the TXS and control groups, but the results of the immediate or delayed recognition test (CANTAB VRM-I recognition and VRM-D, respectively, Table 3) did not. When FSIQ was added to the regression model as a potential confounder, the results of the VRM-I recall subtest did not remain significantly different between the two groups (Table 4).

3.2.3. Visual information processing

The results of the Block Design subtest (for results see Table 2) showed a significant difference between the TXS and the control groups. Our analysis revealed that the results of the PAL subtest did not differ significantly between the TXS and control groups (Table 3).

3.2.4.. Attention

In the TXS group, attention scores were significantly lower than in the control group, with RVP mean latency providing the best indicator of visual sustained attention (Table 3). When FSIQ was added to the regression model as a potential confounder, the results of the RVP subtest remained significantly different between the two groups (Table 4). The

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results of the behavioural categories of the ABCL scales are summarised in Table 5. T-scores on the Attention syndrome scale differed significantly between the TXS group (62.7 SD= 9.13; 95% CI: 59.5 to 65.9) and the control group (56.3 SD= 5.2; 95% CI: 54.4 to 58.2; t(62) = 3.44, p = .001). This difference remained significant even after FSIQ was added to the regression model as a potential confounder (B = -5.03, t = -2.77, 95% CI: -8.66 to -1.40, p = .007, partial eta-squared = .12). In contrast, the DSM-oriented ADHD scale did not differ significantly between the TXS group (60.2 SD= 8.6; 95% CI: 57.1 to 63.9) and the control group (57.0 SD= 5.9; 95% CI: 54.8 to 59.1; p = .087), even after FSIQ was added to the regression model as a potential confounder (B = -2.42, t = - 1.25, 95% CI: -6.30 to 1.46, p = .217, partial eta-squared = .026).

Table 5. Summary of group differences of ABCL results in the triple X syndrome (TXS) and control groups.

	TXS group (n = 33)			Control group (n = 31)			
	Normal Range	Borderline range	Clinical range	Normal Range	Borderline Range	Clinical range	*p*-value†
ABCL Syndrome scale							
Attention problems	22 (66.67%)	7 (21.21%)	4 (12.12%)	29 (93.55%)	2 (6.45%)	0	**.02**
ABCL DSM-oriented scales							
Inattention	27 (81.82%)	6 (18.18%)	0	28 (90.32%)	2 (6.45%)	1 (3.23%)	.26
Hyperactivity-Impulsivity	24 (72.73%)	4 (12.12%)	5 (15.15%)	27 (87.10%)	4 (12.90%)	0	.10
ADHD	25 (75.76%)	3 (9.09%)	5 (15.15%)	27 (87.10%)	3 (9.68%)	1 (3.23%)	.36

† Fisher's exact test.

Abbreviations: ABCL - Adult Behaviour Checklist; ADHD - Attention Deficit Hyperactivity Disorder; DSM - Diagnostic and Statistical Manual of Mental Disorders.

3.2.5.. Executive functioning

Our analysis revealed that the results of the SWM, OTS and IED subtests of the CAN-TAB did not differ significantly between the TXS and control groups (Table 3).

4. Discussion

4.1 . Intro

This study aimed to compare neurocognitive functioning between women with TXS and controls in adulthood (18-65 years). To date, studies have focused on children, adolescents, and relatively young adults with TXS. Only one very small and biased study in relatively young adults partly overlapped with the present study (26-36 years) [10]. Our main findings are that the women with TXS in our study had reduced overall intellectual functioning and scored significantly lower on three out of four WAIS subtests. In addition, we found that the women with TXS did not differ from the control group with respect to visual/episodic memory, verbal recognition memory, or executive functioning, but did differ significantly with respect to attention and motor processing speed.

4.2. General intellectual functioning

Consistent with our hypothesis, and consistent with reports of lower IQ scores in young girls, adolescent girls, and relatively young women with TXS [6,7,10,11,13,16], we found that adult women with TXS also have lower IQ scores compared to the control group. Moreover, we found that the lower degree of general intellectual functioning among the women with TXS was reflected in their lower education levels compared to controls. Thus, additional research is needed in order to examine the relationship between intelligence and occupational adjustment and functioning in women with TXS [38].

Because intelligence is consistently lower in TXS in children, adolescents and adults, there is evidence that the extra X chromosome is related to the lower IQ. The additional X chromosome is rarely passed on the child [1]. Thus, the children of women with TXS often have a normal FSIQ and achieve a higher level of education than their mother. In this respect, FSIQ in the daughters of women with TXS are similar to FSIQ in their

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grandparents and other unaffected members of their mother's family [39]. This may affect family life, and quality of life for family members.

4.3. Psychomotor speed

Based on the results obtained for the Digit Symbol Coding subtest, we found that psychomotor speed was lower in the TXS group than in the control group. Psychomotor speed was assessed using the Digit Symbol Coding subtest and depends on several factors, including attention, executive control, and the speed of cognitive decision-making [40]. Other results in our study support our finding of lower psychomotor speed among the women with TXS, including the CANTAB MOT, and CANTAB RTI data. This decrease in processing efficiency is likely due primarily to a decrease in cognitive processing, reduced motor speed, and/or a decrease in the level of general functioning, although the RTI data suggest that motor processing speed is the principal underlying factor. Interestingly, although the women in the TXS group needed more time than the control group to complete the tests, they made a similar number of errors.

Earlier studies found lower processing speed in girls with TXS compared to boys with a 47,XXY chromosome count [15]. Here, we report that motor processing speed plays a larger role than mental processing speed in adult women with TXS adults. Decreased motor coordination and decreased motor planning have been described in both children and adolescents [9], but have not been studied systematically in adults with TXS. Moreover, decreased psychomotor speed may influence the career [41], daily functioning, and/or quality of life [42]. Workplaces that require little speed but especially correct execution could fit for women with TXS.

4.4. Verbal memory

Verbal deficits in general – and expressive language functions in particular – were previously reported in a longitudinal study involving relatively young adults with TXS [13]. Here, we report verbal memory deficits in the recall part of the immediate test (CANTAB VRM-I recall), but not in the recognition part of the immediate or delayed test (CANTAB VRM-I recognition and VRM-D, respectively). Recognition is generally easier than recall. One major difference between the recall and recognition parts of the test is that cues were provided in the recognition test, which can help with memory retrieval [43]. Thus, women with TXS have more difficulties with memory retrieval compared to controls in the immediate test. It would be interesting to assess memory retrieval in a delayed recall test.

4.5. Visual information processing

We measured visual information processing using the Block Design subtest (Table 2) of the WAIS-III-SV [44] and the PAL subtest of CANTAB (Table 3) [30]. The results of the Block Design subtest demonstrated a significant difference between the TXS and the control group, which is comparable with the results in the study of relatively young adults [13], however, the results of the PAL subtest did show no statistically significant differences. One possible explanation for this difference in results between these two tests may be that we used the conventional – albeit abbreviated – Block Design test in our study, which included time limits and thus implicitly tests processing speed; in contrast, the PAL is less dependent on processing speed. In addition, CANTAB is an automated test battery, whereas the WAIS requires social interactions with the research assistant, which may have affected the results in the TXS group more than in the control group [5]. Visual information processing skills in TXS deserves future research, as it plays an important role in daily life and in choosing a profession [45].

4.6. Attention

Even after we adjusted for FSIQ, our analysis of sustained attention in CANTAB tests revealed lower scores in RVP mean latency in the TXS group compared to the control group. The results of the Attention problems subscale in the ABCL – but not the DSM-

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oriented attention problems scores – are consistent with these results, providing evidence of attention problems based on both objective tests and informant-based reports. In this respect, it is important to note that 5 of the 34 participants in the TXS group (14.7%) had ADHD scores that were in the clinical range, but only one of these participants was taking a stimulant medication for treating ADHD.

The results regarding attention problems in our TXS group are hard to compare with the previously reported results of a study involving 25 children with TXS [46]. Both studies demonstrated problems in attentional functioning. In the previous study in children, the authors found that 44% of the girls with TXS had signs of the inattentive subtype of ADHD based on parent-reported questionnaires. The authors concluded that psychopharmacological treatment of ADHD symptoms may be promising in TXS [46]. However, referral bias may have been a factor in their TXS group, as 6 of the 25 children with TXS (24%) were reported to have seizures [46], which is associated with an increased risk of ADHD, particularly the inattentive subtype [47,48]. In our study, such a referral bias was relatively low, as only one participant in the TXS group was taking an antiseizure medication, and we found no significant difference in FSIQ between the women who were diagnosed with TXS prenatally and the women who were diagnosed postnatally.

Whether psychopharmacological treatment can benefit adults with TXS is currently unknown. In general, the ability to recognise ADHD in women is reduced, as women are generally less likely to present with hyperactivity symptoms and co-existing disruptive conditions [49]. Undertreatment in the particular patient population of TXS women may be even larger due to the low self-esteem [50] and poor social skills [5] among women with TXS [51]. Future studies should therefore attempt to determine whether the attention problems in women with TXS are related to the inattentive subtype of ADHD and/or other factors or conditions. In addition, future studies involving adults with TXS are needed in order to determine whether methylphenidate can improve cognitive functioning in adults with TXS, thus improving their everyday lives [52].

4.7. Executive functioning

We found no significant difference between the TXS and control groups with respect to executive functioning, including strategy, planning, and working memory measured using the CANTAB, as well as working memory measured using the abbreviated Arithmetic subtest of the WAIS-III.

These results are in contrast with results reported in relatively young adults with TXS [13]. This difference may be due to selection bias in the study by Bender et al. as several children deceased and others were lost to follow-up. [10]. This difference may also be due – at least in part – to the use of different methods for assessing working memory. For example, Bender and colleagues used the conventional pencil-and-paper form of the WCST [13], while we used a Tablet-based IED in the CANTAB. Indeed, some groups have reported that the social demands associated with administering the WCST may yield different outcomes when a computer-based administration is used [53,54]. In contrast, other groups reported no apparent differences between the conventional pencil-and-paper and computer-based forms of the WCST and similar tests [55]. In addition, both shyness [1] and social impairments [5] have been reported among individuals with TXS. Taken together, these findings suggest that further study is needed in order to determine whether the form of the test affects the results obtained for women with TXS.

Because our results with respect to executive functioning in women with TXS women differ from previous results in children and relatively young adults [13], it is reasonable to speculate that differences in executive functioning between subjects with TXS and controls may decrease as these girls reach adulthood. Thus, although women with TXS have developmental delays, their final level of executive functioning may reach similar levels in comparison to controls. Maturation of the brain may play a role in the increase in executive functioning in adults with TXS. Moreover, given that executive functioning has been associated with frontal brain areas, both functional and anatomical studies of the brain in

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women with TXS at various ages may provide a plausible explanation for these observations [15].

4.8. The hypothetical role of the cerebellum

Although the most well-recognised function of the cerebellum is to regulate movement, this brain structure also controls the speed and appropriateness of cognitive and emotional processes and is involved in disorders of attention [56]. In addition, the cerebellum also plays a role in the motor functions that mediate speech [57], social functioning [58], and emotion recognition, particularly the recognition of so-called 'negative' emotions [59]. Thus, the attention deficits and reduced psychomotor speed identified in our study may be explained – at least in part – by altered cerebellar function. Indeed, other features commonly associated with TXS that may be explained by altered cerebellar neurodevelopment include social impairments [5], impaired recognition of negative emotions [5], apraxia of speech [3], and hypotonia [3]. Furthermore, cerebellar subregions that are altered in individuals with an extra X chromosome have been linked to motor control and language processing tests [60]. Taken together, these findings suggest that changes in cerebellar function may play a key role in the deficits associated with TXS, with therapeutic implications. For example, non-invasive cerebellar stimulation in healthy adults using transcranial magnetic stimulation was recently shown to dramatically decrease both reaction time and response time when performing a social cognition test [58]. Thus, the cerebellum warrants further attention in women with TXS, particularly with respect to the availability of non-invasive therapeutic options such as cerebellar stimulation.

4.9. Strengths and limitations

The strength of this study lies in the fact that this study, for the first time, has examined a fairly large sample of adults with TXS with a wide range of neuropsychological tests, many of which are not dependent on language skills. In addition, this study had relatively low ascertainment and referral bias.

This study also had several limitations that warrant discussion. First, in the present paper a relatively large number of tests were performed and, thus, there was multiple testing. We agree with Field that Bonferroni is slightly conservative and tends to be too strict when lots of tests are performed [61], in particular in studies with a somewhat exploratory nature like the present study [62]. In combination with the limited power of this study, this would have resulted in not reporting associations that were worth assessing in future studies [63]. When we would have controlled for Bonferroni, the two-tailed Student's *t*-test results of the FSIQ, the RTI Mean simple movement time, the RVP Mean Latency, the RTI Mean five-choice movement time (Table 3), the T-scores on the Attention syndrome scale and group differences on cognitive functioning considering FSIQ as a potential confounder MOT Mean latency (Table 4) remained statistically significant. So, the primary findings of this study "survive" the Bonferroni correction. A second limitation is the cross-sectional nature of the study that limited our ability to study the development of neurocognitive functioning at various timepoints. Third, there is a hypothesis that executive functioning and other measures assessed in the present study in TXS women might differ between different age groups. For two reasons, we did not perform separate analyses to assess this. The number of subjects per age group was too small and there is a risk of bias within the group of TXS patients. The subgroup with a prenatal diagnosis was younger during the study than the subgroup with a postnatal diagnosis. The subgroup with a prenatal diagnosis might function better, than, for example, the subgroup with a postnatal diagnosis because of atypical development. A future longitudinal prospective study would provide valuable insights into the progression of TXS. Fourth, there were some outliers in this study (see Table 3). We excluded these outliers from our analysis of the results of the CANTAB [64]. Outliers seemed to be associated with familiarisation problems, fatigue, smoking behaviour, and/or inadequate understanding of instructions. Fifth, CANTAB does not provide norm scores which hampers comparison with results from previous studies [15]. Furthermore, the majority of women in both groups were

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premenopausal. Thus, the data may not necessarily apply to postmenopausal women with TXS. Furthermore, we used a short version of WAIS-III. To assess differences in VIQ and PIQ between the TXS and control groups the full version of the WAIS would have been preferable. Finally, women under legal guardianship were excluded from the study which may impact the generalizability. However, only two women were actually excluded.

5. Conclusions and further recommendations

Reduced levels of general functioning, decreased psychomotor speed, particularly decreased motor processing speed, and attention disorders can severely limit the education and societal participation of adults with TXS. It is, therefore, important that girls with TXS know that their executive functioning can improve. In this respect, our results may be used to improve the functioning of women with TXS, for example by helping them find suiTable educational support [65] as well as jobs [66] that match their abilities by increasing their own awareness – and the awareness of potential employers – regarding their competencies. This approach will also reduce their risk of low participation in society [67] and decrease their frustration due to their impairments. We therefore recommend that women with TXS undergo a thorough and broad neuropsychological assessment. Future research should address the question whether the level of functioning in the neuropsychological domains may be associated with daily activities, like daily living skills, academic/vocational functioning, and social functioning.

Several suggestions for future research have been discussed above. Impairments in attention and psychomotor speed (particularly motor processing speed), as well as the delayed development in executive functioning, appear to be most relevant findings with respect to neurocognitive functioning in adults with TXS. In addition, further studies are needed in order to determine whether adults with TXS – regardless of a diagnosis of ADHD – may function better with a stimulant medication. Targeted and individualized cognitive remediation could be proposed to increase the functioning in specific neuropsychological domains, e.g. attention, although there is no evidence that these might be helpful in women with TXS [68]. In addition, more research is warranted in order to identify the underlying mechanisms (e.g. motor speed/coordination, relational memory deficits, and/or visual scanning inefficiency) that affect psychomotor speed. Future studies should include linguistic functioning in order to provide a more complete picture of development into adulthood. In addition, longitudinal studies may provide further insights into the differences in executive functioning between girls/adolescents with TXS and women with TXS.

Functional brain studies such as resting-state analysis and network analysis by performing diffusion tension imaging of the cerebellum seem promising [58] with respect to neuropsychological functioning in TXS and may provide important insights into whether cerebellar stimulation can be beneficial in women with TXS.

Finally, the average age of the women in our study was in the early thirties. Given that the results of the Digit Symbol Coding [40] and the Block Design test are age-dependent [69], with lower scores associated with increasing age, additional longitudinal research is needed in order to better understand the effects of ageing in women with TXS [70].

Supplementary Materials: Details regarding the CANTAB tests and subdomains of the CANTAB are provided in the online supplemental materials.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A: List of abbreviations

95%CI = 95% Confidence Interval

ABCL = Adult Behaviour Checklist

ADHD = Attention Deficit Hyperactivity Disorder

ANT = Amsterdam Neuropsychological Tasks

DSM = Diagnostic and Statistical Manual of Mental Disorders

FSIQ = Full-Scale Intelligence Quotient

IED = Intra/Extradimensional Set Shift

ms = milliseconds

MOT = Motor screening test

OTS = One Touch Stockings of Cambridge

PAL = Paired Associates Learning test

PIQ = Performance Intelligence Quotient

RTI = Reaction Time

RVP = Rapid Visual Information Processing test

SD = Standard Deviation

SWM = Spatial Working Memory

TXS = Triple X syndrome

VIQ = Verbal Intelligence Quotient

VRM-D = Verbal Recognition Memory – Delayed

VRM-I = Verbal Recognition Memory – Immediate

WAIS = Wechsler Adult Intelligence Scale

WAIS-III = Wechsler Adult Intelligence Scale-III

WAIS-R = Wechsler Adult Intelligence Scale – Revised

WCST = Wisconsin Card Sorting Test

WISC-R = Wechsler Intelligence Scale for Children – RevisedReferences

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